REMARKS

Pages 6, 8, 9, 15 of the English specification have been amended to correct errors which were produced when the English translation of the original German PCT application was prepared. For example, on pages 6, 8, 15 a binding "compared to" has been amended to read "with respect to" in order to more clearly describe Applicants' disclosure. Claim 13 has been amended to better define the invention. Support for amended claim 13 can be found, for example, in the specification at paragraphs [0011] – [0025]. No new matter is added.

REJECTION OF CLAIMS UNDER 35 U.S.C. §102

Claims 13-17 are rejected under 35 U.S.C. §102(b) as being anticipated by Parmentier *et al.* (U.S. Patent No. 6,228,597; hereinafter "Parmentier"). The Office Action maintains the anticipation rejection based upon Parmentier, alleging that Parmentier anticipates the present invention for the reasons previously stated, and further as evidenced by Weir *et al.* (Handbook of Experimental Immunology in Four Volumes, Volume 1: Immunochemistry, Forth Edition, 1986, pages 34.7-34.8; hereinafter "Weir").

In response, Applicants respectfully point out that Parmentier fails to mention purified autoantibodies isolated from sera of Graves' disease patients by affinity chromatography using a recombinant hTSHr as affinity material. Paremention does not teach a method for determining the amount of thyroid stimulating hormone (TSH) receptor autoantibodies in a human serum or plasma sample comprising: contacting said human serum or plasma sample with TSH receptor (TSHr) that is immobilized on a solid support in the presence of labeled antibodies against the TSH receptor for a time sufficient for the autoantibodies in said human or plasma sample to competitively bind to the TSH receptor; removing unbound labeled TSH receptor antibodies; and determining the amount of TSH receptor autoantibodies in the human serum or plasma sample by measuring the amount of label bound to the TSH receptor. Rather, Parmentier discloses the complete DNA and amino acid sequences of the TSH receptor, and refers to a competition assay that employs experimentally induced antibodies as the competitor, ***not*** naturally occurring ***auto***antibodies isolated from GD patient sera. Thus, Parmentier fails to teach two features of

Applicants' claimed method: 1) affinity-purified autoantibodies, and 2) use of autoantibodies as the competitor.

A patent claim is anticipated by prior art if a single prior art reference discloses every limitation of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of Cal., 814 F.2d 628, 631 (Fed. Cir.1987). If a single claim limitation is missing from the reference, then the reference does not anticipate the claim. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed.Cir.1984).

As amended herein, independent claim 13 is directed to a method for determining the amount of thyroid stimulating hormone (TSH) receptor autoantibodies in a human serum or plasma sample comprising: contacting said human serum or plasma sample with TSH receptor (TSHr) that is immobilized on a solid support in the presence of labeled antibodies against the TSH receptor for a time sufficient for the autoantibodies in said human or plasma sample to competitively bind to the TSH receptor; removing unbound labeled TSH receptor antibodies; and determining the amount of TSH receptor autoantibodies in the human serum or plasma sample by measuring the amount of label bound to the TSH receptor, wherein the labeled antibodies against the TSH receptor are affinity purified polyclonal human autoantibodies from a pool of sera from human Graves' disease patients, purified using a recombinant human TSH receptor.

While referring to Parmentier, it appears the Office Action is failing to distinguish between "antibodies against the TSHR" and "autoantibodies from sera of Graves' disease patients" (see page 3 of the Office Action). The Examiner recites column 9, lines 12-22, highlighting "or with labelled anti-TSHr antibodies". The meaning of TSHr antibodies is described in Parmentier in detail (see column 8, line 59, to column 9, line 11). As is clearly stated, antibodies to the TSHr can be polyclonal and monoclonal, "and may be of animal origin *e.g.* rabbit or mouse" (col. 8, line 62). Further, "use of specific fragments of the TSH receptor allows *the preparation* of antibodies against defined epitopes, and, by using a panel of such antibodies, allows further characterization of the type of disorder present in auto-immune patients." (col. 9, lines 7-11). In other words, in view of Parmentier, the skilled artisan would appreciate antibodies produced when the TSHr or partial peptides of the TSHr are used as immunogens, *i.e.* antibodies formed by immunizing a

suitable animal as *e.g.* a rabbit or a mouse with a TSHr peptide or with portions or special sequences thereof. Further, there is virtually unlimited amount of different "anti-TSHr antibodies".

However, "anti-TSHr antibodies" are not the same as "anti-TSHr autoantibodies." Before the present invention, the characterization of pathological autoantibodies detectable by immunological methods in the circulation of patients (*e.g.* of Graves' disease patients or AITD patients (AITD = autoimmune thyroid disease)) was limited by the very low concentration in patient serum (estimated to be in the range of ng/ml). Because of this low concentration, a skilled artisan would not consider a sample from the human circulation (serum or plasma) as a promising source for antibodies, later to be modified (labelled) and used as reagents in an assay. Rather, antibody reagents used in immunodiagnostic assays are almost exclusively antibodies prepared by immunization of animals with suitable antigenic peptides, and this is what the skilled artisan would understand when faced with "anti-TSHr antibodies" mentioned in Parmentier.

Applicants respectfully note that Parmentier is the first disclosure of the complete DNA and amino acid sequences of the TSH receptor. Additionally, Parmentier contains several proposals how the new sequence information could be exploited, including the preparation of antibodies and assays using the antibodies. According to Parmentier, because of the particular antigenic nature of the TSHr polypeptide, it is useful in preparing anti-TSHr antibodies in an animal, for example, by immunizing a rabbit or mouse with the polypeptide. By such specific reference, Parmentier refers to experimentally induced antibodies ***not*** naturally occurring ***auto***antibodies isolated from GD patient sera. Furthermore, with respect to the use of TSHr in an assay for the quantitative detection of TSH or anti-TSHr antibodies, Parmentier contains no mention of ***auto***antibodies.

For a functioning assay, the proper selection of an anti-TSHr antibody is important. In this respect, it is to be noted that a useful assay should detect autoantibodies, which are heterogeneous (*see* discussion of Morris). Parmentier is completely silent as to how antibody reagents for a functioning assay can be selected.

As additional background, enclosed is a copy of a later published paper (*i.e.* after the

priority date of November 26, 2002 and after the PCT international application filing date of October 31, 2003 of the present application) which is closely related to the work disclosed in the present patent application (Nils G. Morgenthaler et al., "Affinity purification and diagnostic use of TSH receptor autoantibodies from human serum", Molecular and Cellular Endocrinology 212 (2003) 73-79; hereinafter "Morgenthaler"). In Morgenthaler, the prior art concerning anti-TSHr antibodies and their uses is discussed (*see* Introduction, and Discussion sections).

Another copy of a later published paper is enclosed (W. Minich et al., "Antibodies to TSH-receptor in thyroid autoimmune disease interact with monoclonal antibodies whose epitopes are broadly distributed on the receptor", Clin Exp Immunol 2004, 136:126-136; hereinafter "Minich"). In Minich, the authors disclose production of monoclonal antibodies (murine antibodies) binding to certain portions of the human TSHr, which antibodies compete with some of the autoantibodies found in the circulation of Graves' disease patients and AITD patients. That is, said antibodies allow only limited detection of the autoantibodies, and that even a combination of several of such monoclonal antibodies does not give improved detection of autoantibodies in sera of patients. Minich demonstrates that at least until 2004 (*i.e.* well after the priority date of November 26, 2002, and after the PCT international application filing date of October 31, 2003 of the present application), monoclonal anti-TSHr antibodies did not give useful assays for the determination of pathological autoantibodies to the human TSHr.

The present application discusses that there is, among other things, an interference with antibodies reacting with bTSH (bovine TSH) - one problem with the use of labelled bTSH as competitor in assays for autoantibodies to the TSHr in combination with a immobilized recombinant purified TSHr as specific binder is that the specific binder (immobilized hTSHr) rapidly loses its ability to bind the competitor bTSH (*see* the specification, page 6, item 4; page 8, lines 9 to 16; page 15, lines 28 to 33; further see Figure 5 and page 24, last paragraph). However, the presently taught method provides results which are more stable over time and are at least as relevant as results obtained with the use of labelled bTSH as competitor.

Applicants respectfully point to the disclosure at column 14, line 52 to column 15, line 13, for the only teaching in Parmentier that specifically mentions use of autoantibodies

(immunoglobulins) from Graves' disease patients. Applicants respectfully disagree with the Office Action's stance that "…Parmentier teaches the antibody used in the method to detect TSH receptor is purified polyclonal autoantibody against TSH receptor from serum of patients with Graves' disease…" Applicants point out that beginning at column 14, line 51, Parmentier discloses a proof-of-concept experiment to demonstrate that cloned human TSHr can be used to assay for anti-TSHr autoantibodies. The assay disclosed by Parmentier, however, differs from the claimed method. First, Parmentier measures the displacement of radio-labeled TSH (^{125}I-TSH) from the receptor by patient autoantibodies, not, as in the claimed method, the displacement of autoantibodies by autoantibodies; and second, unlike Applicants' invention, Parmentier teaches that the autoantibodies were obtained from patient sera by ammonium sulfate *fractionation* of the patient sera. (*see* example table below comparing Applicants' claimed method with that of Parmentier)

	Parmentier	**Applicant**
What is being measured	displacement of ^{125}I-TSH by patient autoantibodies	displacement of patient autoantibodies by patient autoantibodies
Competition for hTSHr between	^{125}I-TSH and immunoglobulins from GD patients	patient autoantibodies and patient autoantibodies
Preparation of antibodies	ammonium sulfate precipitation of patient sera followed by dialysis	affinity purified using TSHr-affinity column
Purification of antibodies	*no purification* - crude preparation of immunoglobulins/non-specific	*TSHr* affinity-purified/TSHr specific

Applicants point out that ammonium sulfate precipitation is a simple and effective means of *fractionating* proteins. It is based on the fact that at high salt concentrations the natural tendency of proteins not to aggregate is overcome, since the surface charges are neutralized. Charge neutralization means that proteins will tend to bind together, form large complexes and hence are easy to precipitate out by mild centrifugation. Since each protein will start to aggregate at a characteristic salt concentration, this approach provides a simple way of enriching for particular proteins in a mixture, and is used, for example, to isolate immunoglobulins from sera.

Ammonium sulfate fractionation results in a crude preparation of immunoglobulin, not a purified antigen-specific antibody as used in the method as claimed above. As one of skill in the art would recognize, ammonium sulfate fractionation, is generally employed as the initial step in

the isolation of crude antibodies from serum. "Salting out" of polypeptides occurs at high salt concentrations where the salt competes with the polar side chains of the protein for ion pairing with the water molecules, and where the salt reduces the effective volume of solvent. As expected from these observations, the amount of ammonium sulfate required to precipitate a given protein will depend mainly on the surface charge, the surface distribution of polar side chains, and the size of the polypeptide, as well as the pH and temperature of the solution. For example, immunoglobulins, as a group, precipitate at 40–50% ammonium sulfate saturation depending somewhat on the species and subclass.

Antigen specific affinity purification, on the other hand, as known to those of skill in the art and as described at pages 17-19 of Applicants' specification provides antibodies that are, as the name implies, purified based on their antigen specificity. Parmentier fails to suggest, let alone teach, a method for detection of anti-TSHr autoantibodies using anti-TSHr ***auto***antibodies as the competitive detection agent. Moreover, Parmentier fails to even suggest use of purified autoantibodies isolated from sera of Graves' disease patients by affinity chromatography using recombinant hTSHr as affinity material. Parmentier does not contemplate the use of anti-TSHr ***auto***antibodies in an immunoassay and, therefore at least for this reason, cannot anticipate the claimed invention.

The Office Action further rejects the present application, reciting In re Thorpe, 777 F.2d 695, 698 (Fed. Cir. 1985) that "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself....If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Here, Applicants point out that claim 13 of the present application is a process claim, not a product claim. In particular, the claim of the present invention is directed to a method for determining the amount of thyroid stimulating hormone (TSH) receptor autoantibodies in a human serum or plasma sample. As well as contacting and removing steps, another step of the method includes determining the amount of TSH receptor autoantibodies in the human serum or plasma sample. This determining step is achieved by measuring the amount of label bound to the TSH receptor, wherein the labeled antibodies against the TSH receptor are affinity purified

polyclonal human autoantibodies from a pool of sera from human Graves' disease patients, purified using a recombinant human TSH receptor. Thus, contrary to the understanding of the Office Action, Applicants respectfully posit that this is not a case where In re Thorpe applies.

If a single claim limitation is missing from the reference, then the reference does not anticipate the claim. Weir does not add useful specific information to the teachings of Parmentier, and fails to remedy the deficiencies found in Parmentier. Accordingly, for at least the above-identified reasons, Parmentier does not anticipate independent claims 13 and dependent claims 14-17. Thus, Applicants respectfully request that rejection of claims 13-17 under 35 U.S.C. §102(b) be withdrawn.

REJECTION OF CLAIMS UNDER 35 U.S.C. §103

Applicants thank the Examiner for withdrawing the obviousness rejection over Parmentier in view of Brown et al. The Office Action cites new grounds of rejection: claims 13-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Parmentier in view of Morris et al. (Autoimmunity 1994, 17: 287-299; hereinafter "Morris").

The Office Action admits that Parmentier does not teach the labeled anti-TSH receptor autoantibodies obtained by affinity purification against TSH receptor. However, it is alleged that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to perform affinity purification using TSH receptor as the antigen of choice as well as using the affinity-purified anti-TSH receptor autoantibodies as a labeled antibody in the detection assay because Morris discloses using human TSH receptor extracellular domain peptides as the antigen in the affinity chromotagraphy for the purification of anti-TSH receptor autoantibodies. As such, it is alleged that a skilled artisan would have been motivated to use the extracellular domain peptides of the TSH receptor taught by Morris to affinity purify the anti-TSH-receptor autoantibodies because Parmentier taught that the extraceullar domain of the TSH receptor is ideal to prepare antibodies.

PARMENTIER

Parmentier was discussed in detail *supra*. For the same reasons as outlined above, Parmentier does not teach or suggest the present invention as claimed in view of the present amendment.

MORRIS

Morris describes attempts to affinity purify certain anti-TSHr autoantibodies using synthetic human TSHr peptides. As is well known to a skilled person, peptides representing partial amino acid sequences of a long peptide as the TSHr are recognized only by such antibodies which bind to linear continuous epitopes. In Morris, three different peptides, each of about 20 amino acids, were found to bind to IgG from Graves' disease patients (peptides 181-200, 376-394, and 629-639). There were, further, clear differences between sera (IgG) of different patients.

Morris discloses that autoantibodies binding to such linear peptides represent only a small fraction of the pathologically relevant autoantibodies present in Graves' disease patients. Morris states that "the epitopes for TSHr auto-antibodies are likely to be largely conformational in nature and, as such, an individual peptide as those used in our and other studies probably represent only a portion of a much larger binding surface." (*see* discussion and in particular page 294). For an assay which aims to detect many autoantibodies in an unlimited population of patients, affinity purified autoantibodies obtainable by the method of Morris clearly are of no use.

PARMENTIER IN VIEW OF MORRIS

The Supreme Court in the KSR decision stated that the analysis supporting a rejection for obviousness be made explicit and that rejections can not be sustained by mere conclusory statements but, instead, there must be an articulated reason with some rational underpinning to support the legal conclusion of obviousness. The USPTO guidelines lists seven rationales used to support a conclusion of obviousness, including: (a) combining prior art elements according to known methods to yield predictable results; (b) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and (c) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to

modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Here, a PHOSITA would not have recognized that the results of combining Parmentier with Morris were predictable for the reasons outlined above. Moreover, the presently taught method would not be obvious to try because, *inter alia*, Parmentier observed that one of two autoantibody preparations from GD patients examined (only two were tested) exhibited limited ability to displace labeled TSH under the conditions of the assay (GD2 in Figure 10; see column 14, line 52 to column 15, line 13, for the only teaching in Parmentier that specifically mentions use of autoantibodies (immunoglobulins) from Graves' disease patients). Thus, based on this teaching, one of skill in the art would not conclude that the use of GD patient-derived autoantibodies would be a desirable competitor/reporter in an assay system to detect anti-TSHr autoantibodies. Indeed, this may be construed by some as teaching away from practicing the method of the presently taught invention.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994); see KSR, 550 U.S. 398, 416 (2007) (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). A reference should be considered in whole, and portions arguing against or teaching away from the claimed invention must be considered. Bausch & Lomb, Inc. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). Therefore for this additional reason, the obviousness rejection based upon combining the primary Parmentier reference with Morris is improper and should be withdrawn.

Parmentier neither teaches nor suggests a method for detection of anti-TSHr autoantibodies using anti-TSHr ***auto***antibodies as the competitive detection agent. Moreover, Parmentier fails to even suggest use of purified autoantibodies isolated from sera of Graves' disease patients by affinity chromatography using a functional (*i.e.* correctly folded) recombinant hTSHr as affinity material, let alone teach the method of the presently claimed invention.

One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fritch, 972 F.2d 1260 (Fed. Cir. 1992). Using the inventor's success as evidence that one of ordinary skill in the art would have reasonable expected success represents an impermissible use of hindsight. Life Technologies, Inc. v. Clontech Laboratories, Inc. 224 F.3d 1320 (Fed. Cir. 2000). It is impermissible to engage in a hindsight reconstruction of the claimed invention by using the applicant's structure as a template and selecting elements from references to fill in the gaps. In re Gorman, 933 F.2d 892 (Fed. Cir. 1991).

Morris cannot compensate for the deficiencies in the teachings of Parmentier. Rather, Morris describes attempts to affinity purify certain anti-TSHr autoantibodies using synthetic human TSHr peptides. Morris discloses that autoantibodies binding to such linear peptides represent only a small fraction of the pathologically relevant autoantibodies present in Graves' disease patients. Further, the autoantibodies of the present invention are purified using a functional recombinant TSHr bound to an affinity material. This specific purification procedure would indicate to one of ordinary skill in the art that the purified autoantibodies of the claimed invention are distinguished from the autoantibody fractions prepared by Morris which recognize only continuous linear peptide epitopes. As such, nothing in Morris remedies the deficiencies found in Parmentier as outlined *supra*.

Therefore, at least for this additional reason, Parmentier in view of Morris does not teach or suggest the present invention. As such, Applicants respectfully request that rejection of claims 13-17 under 35 U.S.C. §103(a) be withdrawn.

REJECTION UNDER DOUBLE PATENTING

Claim 13 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of Parmentier. The Examiner indicates that although claim 13 of the present invention and claim 9 of Parmentier are not identical, they are not patentably distinct.

The doctrine of double patenting seeks to preclude timewise extension of the right to exclude by preventing the same inventor or assignee from obtaining a second patent on the same

invention ("same invention" double patenting) or on an obvious variant thereof ("obviousnesstype" double patenting). The appropriate inquiry is whether the claims in the pending application are directed to subject matter that is "different but not patentably distinct from the subject matter claimed in the prior patent." In re Goodman, 11 F.3d at 1052, 29 U.S.P.Q.2d 2010, 2015 (Fed.Cir.1993). In an obviousness-type double patenting rejection, the claim(s) of the first patent are applied alone or as a primary reference combined with other references to illustrate the unpatentability of the claims in the second patent or application.

Claim 5 of Parmentier is directed to a biologically active preparation of human TSH receptor in the form of an isolated recombinant polypeptide expressed by a transformed host cell, said polypeptide comprising the amino acid sequence set forth in SEQ ID NO:59, and being free of impurities associated with detergent-solubilized thyroid membrane preparations.

Claim 9 of Parmentier is directed to a process for the quantitative detection of anti-thyrotropin receptor antibodies (anti-TSHr) in a biological sample comprising the steps of: contacting a polypeptide according to claim 5 with the biological sample suspected of containing anti-TSHr antibodies, incubating with labelled TSH, or with labelled anti-TSHr antibodies; measuring the remaining, bound labelled TSH or bound labelled anti-TSHr antibodies, after competition between the labelled and unlabelled species; and correlating results from the measuring step to the presence of anti-TSHr antibodies. Thus, this claim is not concerned with anti-TSHr autoantibodies.

In contrast, as amended herein, claim 13 of the present application is directed to a method for determining the amount of thyroid stimulating hormone (TSH) receptor autoantibodies in a human serum or plasma sample comprising: contacting said human serum or plasma sample with TSH receptor (TSHr) that is immobilized on a solid support in the presence of labeled antibodies against the TSH receptor for a time sufficient for the autoantibodies in said human or plasma sample to competitively bind to the TSH receptor; removing unbound labeled TSH receptor antibodies; and determining the amount of TSH receptor autoantibodies in the human serum or plasma sample by measuring the amount of label bound to the TSH receptor, wherein the labeled antibodies against the TSH receptor are affinity purified polyclonal human autoantibodies from a pool of sera from human Graves' disease patients, purified using a recombinant human TSH

receptor.

Therefore, claim 13 of the present application as amended herein is neither anticipated by or an obvious variation of the claims of claim 9 of Parmentier. Applicants further point to the distinctions highlighted *supra* between the present application and Parmentier, which further indicate that there would be no extension of the right to exclude. Accordingly, Applicants respectfully request withdrawal of this double patenting rejection.

CONCLUSION

There being no other outstanding issues, it is believed that the application is in condition for allowance, and such action is respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

The undersigned hereby authorizes the Commissioner to charge any fee insufficiency and credit any overpayment associated with this submission to Deposit Account No. 08-1935.

Respectfully submitted,

/Shahrokh Falati/

Date: April 27, 2010

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Enclosures: [Background art: Morgenthaler];
[Background art: Minich];
[Background art: Thermo Scientific article on Affinity Purification]

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